Genome-Wide Association Analysis Identifies Dcc as an Essential Factor in the Innervation of the Peripheral Vestibular System in Inbred Mice.

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Public Summary:
In this manuscript, we have, for the first time, used association analysis with correction for population structure to map loci for vestibular functional variation in inbred strains of mice.

Scientific Abstract:
This study aimed to investigate the genetic causes of vestibular dysfunction. We used vestibular sensory-evoked potentials (VsEPs) to characterize the vestibular function of 35 inbred mouse strains selected from the Hybrid Mouse Diversity Panel and demonstrated strain-dependent phenotypic variation in vestibular function. Using these phenotypic data, we performed the first genome-wide association study controlling for population structure that has revealed two highly suggestive loci, one of which lies within a haplotype block containing five genes (Stard6, 4930503L19Rik, Poli, Mbd2, Dcc) on Chr. 18 (peak SNP rs29632020), one gene, deleted in colorectal carcinoma (Dcc) has a well-established role in nervous system development. An in-depth analysis of Dcc-deficient mice demonstrated elevation in mean VsEP threshold for Dcc (+/-) mice (-11.86 dB) compared to wild-type (-9.68 dB) littermates. Synaptic ribbon studies revealed Dcc (-/-) (P0) and Dcc (+/-) (6-week-old) mice showed lower density of the presynaptic marker (CtBP2) as compared to wild-type controls. Vestibular ganglion cell counts of Dcc (-/-) (P0) was lower than controls. Whole-mount preparations showed abnormal innervation of the utricle, saccule, and crista ampullaris at E14.5, E16.5, and E18.5. Postnatal studies were limited by the perinatal lethality in Dcc (-/-) mice. Expression analyses using in situ hybridization and immunohistochemistry showed Dcc expression in the mouse vestibular ganglion (E15.5), and utricle and crista ampullaris (6-week-old), respectively. In summary, we report the first GWAS for vestibular functional variation in inbred mice and provide evidence for the role of Dcc in the normal innervation of the peripheral vestibular system.